ONE MEDICINE

MONKEYPOX, AFRICAN RODENTS, PRAIRIE DOGS, FERRETS, AND INFLUENZA

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Historical Perspective

Until May 2003, human monkeypox (MPX) was an obscure sporadic zoonosis confined to the equatorial rain forests of Africa. The disease, which clinically resembles smallpox (SPX), is caused by an orthopoxvirus genetically similar to *Variola major* and *V. minor*, the etiologic agents of human smallpox. The natural history of MPX is not fully understood but evidence suggests that rodents serve as the primary viral reservoir. Monkeys and other primates, including humans, are susceptible to the disease, but are incidental hosts. Although routes of exposure and transmission have not been clearly delineated, most human cases are associated with animal contact. Increased trade in bushmeat is one possible emerging, but as yet unproven, risk factor for MPX in enzootic areas.

Monkeypox was first recognized in1958 as an exanthem in captive primates. Over the next 10 years, nine additional outbreaks were observed in primates and other captive animals in zoos and animal importation centers in Europe and the United States (US). The first human case, a nine month-old child who had not been vaccinated against smallpox, was identified in 1970 in Zaire (formerly the Belgian Congo and presently the Democratic Republic of the Congo [DRC]). Following the eradication of SPX in sub-Saharan Africa, between 1970 and 1994, about 400 cases of MPX were reported from the tropical rain-forested countries of West and Central Africa. Approximately 95% of these were reported from Zaire during a period of intense surveillance from 1982-1986. Epidemiologic and laboratory studies conducted during that period provide the foundation of our knowledge about MPX in the natural setting.

Monkeypox cases tend to occur singly or in small clusters, with the majority of human infections attributable to contact with infected animals. Compared to SPX, MPX is less virulent and less transmissible to humans. The incubation period for MPX, like that of SPX, is about 12 days (range 7-17 days). Clinically, MPX resembles the ordinary or modified forms of SPX. Symptoms include fever, headache, muscle aches, backache, swollen lymph nodes, a general feeling of discomfort and exhaustion, chills and/or sweats, sore throat, cough, and shortness of breath. Lymphadenopathy, observed in up to 90% of MPX cases and rarely in SPX, is a key distinguishing feature. It occurs early in the disease course, before the onset of rash. In unvaccinated African populations, the rash of MPX is similar to that of SPX. Following a prodromal period of 1-4 days, a maculopapular rash appears. Over the next 2-4 weeks, the lesions progress from macules to papules, vesicles, and pustules, followed by umbilication, scabbing, and desquamation. Like SPX, the rash in MPX starts on the trunk and spreads peripherally, often involving the palms and soles. Lesions in both diseases tend to be deep and of homogenous stage (same stage) when observed. These features (deep, homogenous lesions and centrifugal distribution with involvement of the palms and soles) are key distinguishing clinical findings of SPX and MPX compared to chickenpox (varicella) which is characterized by superficial, heterogenous lesions (lesions in different stages) and centripetal distribution in which involvement of the palms and soles occurs only rarely.

The routes/mechanisms of person-to-person transmission for MPX are also similar to those of SPX, but the risk of secondary transmission for MPX appears to be significantly lower, in the range of 8-28%. Illness due to MPX lasts from 2 to 4 weeks. The case fatality ratio (CFR) of MPX is lower compared to SPX. Among unvaccinated populations in West Africa, the CFR for MPX varies between 1% to 10%, although it may be higher in young children. In contrast, the historical CFR for SPX (*Variola major*) among unvaccinated populations ranged from 20-50%.

Due to the genetic similarities between the SPX and MPX orthopoxviruses, smallpox vaccination with *Vaccinia* virus provides protection against both diseases. It has been suggested that the primary reason MPX has been an uncommon disease in equatorial Africa is due to residual humoral immunity from SPX

vaccination in the 1950's and 60's. Although residual immunity from SPX vaccination is likely a protective factor in some areas, studies indicate that human MPX is uncommon even in enzootic areas where the rate of historical smallpox vaccination is known to be low.

Importation of Monkeypox into the US

As recently as 2000, one public health reference (APHA, Chin) put human MPX in the following perspective: "There is no evidence that monkeypox will become a public health threat outside of enzootic areas." That assessment proved to be inaccurate following a shipment of 762 exotic rodents (50 Gambian giant rats, 510 dormice, 53 rope squirrels, 47 tree squirrels, 100 striped mice, and 2 brushtail porcupines) destined for the pet trade that were imported into the U.S. from Accra, Ghana on April 9, 2003. Here is what we now know.

Following their arrival in Texas, the African rodents were parceled out to animal distributors in Texas, New Jersey, and Iowa. A group of Gambian giant rats and dormice from the Iowa distributor was then shipped to an Illinois distributor who happened to have 200 prairie dogs at his facility. It appears the prairie dogs at the Illinois facility were subsequently infected through close contact with the Gambian giant rats and dormice. The infected prairie dogs then served as disease vectors, transmitting MPX to humans who acquired them as pets or otherwise handled them. Symptoms and signs in the MPX-infected rodents included cough, purulent ocular and nasal discharges, swollen lymph nodes in the arms and legs and papular/vesicular rash. Subsequent testing of some of the rodents from the Ghanaian shipment by the Centers for Disease Control and Prevention (CDC) confirmed MPX infection in Gambian giant rats, dormice, and rope squirrels. Of the 762 animals in the shipment, as of July 2003, about 465 were known to be dead, 121 alive and about 178 (mostly dormice) lost to follow-up. Although latent viral infection in animals is not known to occur, it has not been completely ruled out either. Images of dormice and the other implicated rodent species may be found in the CDC embargoed animals link in the reference list.

Human Illness, Epidemiologic Investigation, and Use of Smallpox Vaccine

The first human cases of domestic MPX were identified in Illinois and Wisconsin in mid and late May 2003. As of July 8, 2003, 71 cases of MPX had been reported to the CDC by the following states: Wisconsin (39), Indiana (16), Illinois (12), Missouri (2), Kansas (1), and Ohio (1). Of these, 35 were laboratory confirmed by CDC and 36 were classified as suspect or probable cases under investigation by local and state health departments.

Most cases experienced a mild, self-limited febrile rash illness. Among the 35 laboratory-confirmed cases, 34 (97%) experienced rash, 29 (85%) fever, 27 (77%) respiratory symptoms, and 24 (69%) lymphadenopathy. Sixteen laboratory-confirmed cases were hospitalized, some only for isolation precautions. However, two children developed serious illness. One child developed encephalitis, a rare complication of monkeypox, and required intensive care for 14 days. The other child required hospitalization due to painful cervical and tonsillar lymphadenopathy and diffuse pox lesions which even involved the oropharynx. Both children recovered and no deaths were associated with the outbreak (CDC/MMWR and Nalca et al, 2005).

Rash distribution included the head, trunk, and extremities, with initial and satellite lesions occurring on the palms, soles, and extremities. Many cases only developed localized lesions on the hands and fingers after handling infected animals. In most cases, the rash progressed through the stages of vesiculation, pustulation, umbilication, and encrustation. Early lesions ulcerated in some patients. Interestingly, only one case, a child, developed a generalized rash illness similar to that experienced by Africans in the Congo basin. The reason for this disparity in clinical presentation is unclear but may be due to differences in virus strain or due to inoculation of the skin, following a bite or scratch by an infected prairie dog, in contrast to inhalation of the virus (CDC/MMWR and Nalca et al, 2005).

For more information on the outbreak case definition, criteria for laboratory confirmation, and progression of the investigation, see the CDC case definition, laboratory, and MMWR links in the reference list.

Smallpox vaccine is recommended for those investigating animal or human monkeypox cases, health care workers and others either caring for, or having close or intimate contact with, infected people or animals, and laboratorians handling specimens that may contain MPX virus. According to the CDC, vaccine may be protective when given up to 14 days after exposure to monkeypox. Additional information on treatment and vaccination may be found in the CDC treatment and vaccination links in the reference list.

Impact of the Outbreak in North Carolina

Fortunately, none of the imported African rodents or prairie dogs infected at the Illinois facility was traced to North Carolina. Nevertheless, NC was subject to the June 11, 2003, joint CDC/FDA order banning the interstate and intrastate movement of prairie dogs except for the purpose of evaluation/treatment by a veterinarian. This caused problems for pet stores, individuals, and others who were unable to legally sell, transport, or otherwise move them. Despite requests by governmental agencies that people not release their captive prairie dogs into the wild, there was at least one instance where that occurred in NC. Such action could result in the establishment of feral prairie dog colonies. Additionally, release of any prairie dogs associated with the imported African rodents into their natural Midwestern habitats could introduce MPX virus into native US prairie dog (or other wild rodent) populations.

On November 4, 2003 FDA and CDC issued an interim final rule (effective November 5, 2003) replacing the June 11, 2003 joint order. It prohibits, until further notice, the capture, offer to capture, transport, sale, barter, exchange, distribution, offer to distribute, or release into the environment of prairie dogs and African rodents. The rule applies to both living and dead animals. The only exceptions are movement to a veterinarian or animal control officer for the purpose of care, quarantine, or destruction. Persons, pet stores/dealers, or institutions needing to move animals for other reasons must apply to the FDA for an exemption. The rule is not intended to pre-empt more restrictive state or local regulations already in place, but such regulations cannot permit something the rule prohibits. Further details on the interim final rule and procedures for applying for an exemption may be found on the FDA and CDC websites listed in the reference section.

The best evidence to date suggests that the infectivity and incubation period of MPX is three months or less. Although it is reassuring that no more domestic cases of MPX have occurred in animals since July 20, 2003 (the date of last animal death), the ban on movement of prairie dogs and African rodents in the US continues. Additionally, the ban on the importation (and exportation from the US) of living or dead rodents endemic to Africa continues indefinitely. In 2004, US Fish and Wildlife Agency officers confiscated an illegal shipment of smoked West African rodents in Atlanta purportedly destined for Charlotte, NC for distribution to local West African food markets. It is important to understand that only those products that have undergone heat or chemical treatment to destroy infectious agents, and fully taxidermied specimens constitute the only exceptions to the import ban. However, following appropriate application, import and export exemptions for specified rodents may be issued for legitimate scientific, educational, or exhibition purposes.

Emerging Public Health Concerns

The recent MPX outbreak in prairie dogs and humans has demonstrated the great costs associated with unregulated importation of exotic animals and translocation of native wildlife species for the pet trade. We know that prairie dogs are vectors for tularemia, plague (via infected fleas), MPX, and possibly salmonellosis. Although prairie dogs were the innocent bystanders in the MPX outbreak of 2003, the practice of vacuuming these animals out of their burrows and selling them into the pet trade nationally and internationally now deserves closer scrutiny. Additionally, although some claim prairie dogs make good pets, knowledgeable veterinarians testify that males especially become aggressive at sexual maturity, biting their owners and others who handle them. In North Carolina and many other states, each bite to a human that is reported must be followed up by the local animal control agency. Investigation often requires consultation with public health veterinarians and the state's public health laboratory, especially when rabies

must be ruled out. Additionally, a single human case of prairie dog-associated tularemia or plague would trigger an epidemiologic investigation and notification of appropriate state and federal agencies.

To begin addressing the public health issues surrounding the trade in exotic and native wildlife, in June 2003, the Council of State and Territorial Epidemiologists (CSTE) Infectious Diseases Committee adopted a resolution titled: *Developing Importation and Exportation Restrictions on Exotic and Native Wildlife with Potential Adverse Impact on Public Health*. Additionally, on July 17, 2003, the CDC provided testimony (CDC's Role in Zoonotic Disease Outbreaks) to the CSTE Committee on Environment and Public Works. New regulatory measures may be enacted in the near future to minimize emerging public health risks associated with the international trade in wildlife.

Monkeypox as a Risk to Native North American Wildlife

Now the black-footed ferret comes into the picture. Ferrets are members of the mustelid family which also include weasels, badgers, stoats, and otters. There are three species of ferrets, the Siberian (*Mustela eversmannii*, also known as the Steppe polecat), the European (*Mustela putorius*, also known as the European polecat), and the North American black-footed ferret (*Mustela nigripes*). Fossil evidence indicates that the North American species descended from the Siberian ferret after it crossed the land bridge during the Pleistocene Period. The domestic ferret (*Mustela putorius furo*), commonly bred and sold as a pet here in the US, most likely originated from the European polecat.

When Lewis and Clark undertook their legendary journey in 1803, prairie dogs and ferrets, their natural predators, were prominent fixtures of Midwestern prairie ecology. In the late 1800's, prairie dogs could be found in great numbers on an estimated 700 million acres in the Great Plains, and at the turn of the century their population was estimated at 5 billion. However, by the 1950's, their habitat had decreased to a few million acres. Following extensive loss of habitat and various extermination programs, prairie dog populations plummeted; a rapid decline in ferret populations soon followed. By the 1960's, only one small ferret population was known to exist in southwestern South Dakota. In 1967, the black-footed ferret was listed as a federally-endangered species and, in 1970, it was thought to be extinct in the wild. The last captive black-footed ferret died in 1979. Then, in 1981, a rancher's dog killed one near Meeteetse, WY, following which a small population (estimated at 129 individuals in 1984) was discovered. The reprieve was short-lived, however. An outbreak of plague decimated the local prairie dog population; shortly thereafter, the newly-discovered ferret population crashed following an outbreak of canine distemper. In 1985, six ferrets were captured to initiate a captive breeding program but all six died within a short period from canine distemper. The remaining 18 ferrets were captured between 1985 and 1987 for a captive-breeding program at the Wyoming Game and Fish Department's Sybille Research Facility where they were quarantined and vaccinated for distemper. Against severe odds, all 18 survived. Initial efforts at breeding and rearing of kits proved frustrating, but subsequent efforts were highly productive. By 1998, captive breeding facilities participating in the Species Survival Plan (SSP) for the black-footed ferret included six zoos and the US Fish and Wildlife Service's National Black-footed Ferret Conservation Center. In that year alone, 425 kits were born of which 321 survived.

Captive propagation of what was once North America's most endangered mammal has been so successful that they have been reintroduced into areas of their native range in six states (Arizona, Colorado, Montana, South Dakota, Utah, and Wyoming) and Mexico. Although the ferrets are reproducing in the wild and appear to be thriving in some areas (the 2006 estimated wild population is 700), the establishment of self-sustaining populations has been hindered by continued loss of prairie dog habitat and the presence of sylvatic plague which is decimating many prairie dog colonies. In addition to depleting prairie dogs, the primary food source for black-footed ferrets, plague also poses a direct risk to ferrets which were once thought to be immune. After a black-footed ferret in Wyoming contracted plague and died, experimental plague testing on black-footed/Siberian hybrids demonstrated 100% mortality.

The black-footed ferret is critical to restoring the balance of nature where the prairie dog lives. The ferrets live in prairie dog burrows and 90% of their diet is comprised of prairie dogs. A single ferret family requires about 100 acres of prairie dog colony for sustenance. In the absence of predators, prairie dog

populations can increase dramatically; this favors enzootics of tularemia and plague, the latter of which was introduced into the US in 1899.

Fortunately, the ban on prairie dog movement, imposed for public health reasons, also served to prevent the introduction of MPX into the North American prairie dog and other native rodent populations, and may have protected the black-footed ferret from this disease. Because exhibition, captive breeding and reintroduction of black-footed ferrets often involves translocation of prairie dogs as a food source, state agencies, zoos and other institutions involved in these activities were subject to the prairie dog movement restrictions in the joint CDC/FDA order. These entities continue to be subject to restrictions in the current interim rule and must apply for an exemption. Black-footed ferret captive breeding and exhibition activities are ongoing in Virginia, Kentucky, Wyoming, Colorado, and Canada. Reportedly, several private facilities in NC maintain breeding colonies of prairie dogs.

Biodiversity and Human Health

One might ask at this point, "What good are ferrets anyway?" This question gets to the heart of the importance of biodiversity to human health. The enormous value of plants, animals and microbes to the diagnosis, treatment, and prevention of human disease cannot be underestimated. For example, DNA polymerase, a heat-stable enzyme isolated in the 1960's from *Thermus aquaticus*, an obscure bacterium cultivated from a hot spring in Yellowstone Park, is the foundation for the polymerase chain reaction (PCR), a molecular technique which has revolutionized genetic disease diagnosis, pathogen detection, and genome sequencing. Over 57% of the 150 most commonly prescribed medicines used today are derived from natural products, constituting 40 billion dollars worth of pharmaceuticals sold annually. Many of our first generation antibiotics (including penicillin, cephalosporin, streptomycin, neomycin, erythromycin, and amphotericin) were isolated from fungi or other microbes. Pit viper venoms were the source of ACE inhibitor and other antihypertensives. The *Vinca* alkaloids, vincristine and vinblastine, derived from the rosy periwinkle, have produced remission rates as high as 99% for acute lymphocytic leukemia (the predominant form of childhood leukemia) and 80% for Hodgkin's lymphoma. Tamoxifen, derived from taxol, a chemical isolated from a fungus found growing on the Pacific yew, has been utilized extensively in the treatment and prevention of breast and ovarian cancers in women. Numerous other examples of naturally-derived medicines used as anti-hypertensive, anti-inflammatory, anti-clotting, anti-tumor, and analgesic agents can be cited. Recently, several naturally-dervived products were demonstrated to be potent inhibitors of human immunodeficiency virus (HIV) *in vitro.*

Moving up the phylogenetic tree, many animal species serve as models for understanding the pathogenesis and transmission of human disease. Why is it that chimpanzees are not susceptible to infection by HIV? The answer to that question lies in the origin of HIV and the nature of the chimpanzee's immune system compared to that of humans. Other animal species provide important insights into immune mechanisms.

As noted above, ferrets are highly susceptible to canine distemper virus. The following historical account, taken from the 2000 Mill Hill Essay by Carver and Skehel, is illustrative. Prior to 1930, distemper was a devastating illness in young dogs, infecting most and killing more than half. Those that survived often were afflicted with "hard pad" (thickening of the nose and footpads) and "old dog encephalitis" (somewhat analogous to canine senile dementia). In the 1920's, British pathologist Patrick Laidlaw and veterinarian George Duncan used ferrets as models during their development of a vaccine for canine distemper at the Rhode's Farm (an outstation for the National Institute of Medical Research in Mill Hill, England). In a series of careful experiments, they observed that chemically-inactivated vaccine derived from virus obtained from infected dogs protected dogs better than ferrets; similarly, vaccine derived from virus obtained from infected ferrets protected ferrets better than dogs. They then observed that long-lasting immunity was achieved by infecting animals with live virus two weeks after vaccination with inactivated virus. By 1929, they had developed their distemper vaccine, which was subsequently commercially produced and marketed by Burroughs Wellcome and Co.

Pandemic influenza struck England in1918-1919 on the heel of World War I. At the time, the cause of influenza was unknown and the responsible infectious agent would not become known for another 15 years. During the severe influenza season of 1933, several ferrets at the Rhodes Farm, which were being

studied for distemper immunity following vaccination, developed the same symptoms of coughing and sneezing as their influenza-infected researchers. Although not previously known, the ferrets were also susceptible to human influenza and had contracted the illness from the scientists. This chance discovery by Patrick Laidlaw, Christopher Andrewes, and Wilson Smith, that ferrets could serve as an animal model for human influenza, led to additional experiments by William Elford et al in which the human influenza virus was isolated and characterized, and early attempts to develop a vaccine. Researchers also observed during those early years that influenza viruses changed from year to year and that these changes could be detected by laboratory tests on sera collected from infected ferrets. To this day, antibodies collected from influenza-infected ferrets are used to distinguish currently circulating human influenza viruses from those of previous years. These studies serve as the basis for yearly updating of multivalent influenza vaccine to enhance our bodies' ability to make antibodies to the new antigens present in circulating strains.

In 2006, the ferret is still being used as a model to help us understand the potential for increased transmissibility of avian influenza virus in humans. Efficient and sustained human-to-human transmission of H5N1 avian influenza viruses is felt to be the sole remaining property necessary for initiation of a pandemic. Just this year, in a series of experiments conducted at CDC, researchers infected ferrets with hybrid influenza viruses genetically engineered to mimic genetic shift, potential gene reassortments that might occur naturally. Genes from human H3N2 influenza virus were added to genes from H5N1 avian influenza virus. Ferrets infected with the hybrid viruses were placed in close proximity to uninfected ferrets to assess transmission. In the ferret model, human H3N2 virus transmits efficiently between ferrets; avian H5N1 virus does not. The recent experiments at CDC demonstrated that the hybrid viruses did not transmit easily, and actually caused less severe disease than that caused by H5N1, suggesting that naturally occurring genetic reassortment of H5N1 might result in a less virulent virus with reduced transmissibility. In another experiment designed to mimic genetic drift, the same researchers passed hybrid virus through a series of ferrets to determine if cumulative genetic change might result in increased transmissibility. Only one genetic change was observed and it did not increase transmissibility (Maines et al 2006; CDC).

One Medicine

The "One Medicine" concept is based on the premise that human medicine and veterinary medicine are inextricably linked. As history demonstrated with canine distemper, investigations into the etiology and treatment of animal diseases can benefit both animals and humans. Similarly, our understanding and treatment of many human diseases can benefit animals. Although the ferrets involved in the distemper and influenza studies presented above were domesticated strains of the European ferret, who would have thought that the distemper vaccine developed in 1929 using the domestic ferret would be used today to help protect its endangered North American cousin, or that human influenza vaccines could serve the same role?

Today, the world faces a host of emerging and re-emerging zoonotic diseases that are directly or indirectly linked to a wide variety of factors. These factors and some of the linked diseases include the following:

- Human overpopulation, crowding and poverty with attendant lack of basic sanitation and protective living conditions that prevent daily exposure to disease vectors:
  [plague, typhus, malaria, mosquito-borne/arboviral diseases (yellow fever, dengue, Japanese encephalitis (JE) and other mosquito-borne encephalitides), Chagas disease, rabies/lyssavirus encephalitis, rat bite fever]
- Regional and transglobal movement of wildlife, pets, livestock, other domestic animals and animal products:
  [bovine spongiform encephalopathy (BSE) and other transmissible spongiform encephalopathies (TSEs), psittacosis, tularemia, plague, anthrax, brucellosis, rabies, severe acute respiratory syndrome (SARS), monkeypox (MPX), reptile-associated salmonellosis, neuroinvasive West Nile Virus (WNV) and avian influenza (AI)]
- Increased reliance on bush meat (especially by burgeoning populations in developing countries) and other wildlife (both terrestrial and aquatic) as food sources:
  [anthrax, viral hemorrhagic fevers (Ebola and Marburg), HIV/AIDS, MPX, SARS, AI, tularemia, trichinellosis]

- Co-mingling of wildlife and livestock and pets:
  [anthrax, brucellosis, bovine tuberculosis (TB), SARS, AI, MPX, BSE and other TSEs, shigatoxin-producing *E coli* (STEC)]
- Intensive livestock farming, overuse of antibiotics, and contamination of livestock feed:
  [BSE/v-CJD, Nipah/Hendra virus encephalitis, AI, cryptosporidiosis, STEC, salmonellosis and campylobacteriosis]
- Increased international travel (and ecotourism) resulting in increased proximity/interactions among wildlife, pets, livestock and human populations:
  [rabies, AI, SARS, leptospirosis, malaria, arboviral diseases, cryptosporidiosis, giardiasis]
- Urban-to-rural migration, particularly in developed countries, resulting in increased exposure to ticks, fleas, and wildlife:
  [Lyme borreliosis, RMSF, ehrlichiosis, plague, tularemia, rabies]
- Environmental degradation, particularly tropical deforestation with resultant flooding and influx of insect and rodent vectors into newly cultivated/populated areas:
  [leishmaniasis, malaria, mosquito-borne/arboviral diseases, Nipah virus encephalitis, viral hemorrhagic fevers (Lassa, Ebola, Marburg, Manchupo/Bolivian, Junin/Argentinian), leptospirosis]
- Loss of biodiversity resulting in increases in the in the number and geographical distribution of zoonotic disease vectors and a decrease in their predators:
  [arboviral diseases, Lyme disease, plague, tularemia]
- Regional and global climate change:
  [dengue, Ross River virus and other mosquito-borne/arboviral encephalitides, leishmaniasis, hantavirus pulmonary syndrome (HPS)]

And, here are some statistics to keep in mind: Of 1,415 pathogens catalogued by Taylor et al in 2001, 62 % were of zoonotic origin. Scientists at the CDC and elsewhere have determined that approximately 75% of emerging infectious disease pathogens are zoonotic. Many emerging zoonotic diseases, such as avian influenza, SARS, the viral hemorrhagic fevers, the arboviral diseases, hantavirus pulmonary syndrome, and Nipah/Hendra virus infection/encephalitis present formidable, and, in some cases, long term challenges to human and veterinary medicine and public health. The challenges become more complex when one considers that, in addition to anthrax, plague, tularemia, and the viral hemorrhagic fevers, at least 15 other zoonotic agents are considered potential bioterrorism agents. Today, more than ever, the concept of "One Medicine" and the epidemiologic triad of "Host, Environment, and Disease" must serve as our compass for evaluating and responding to emerging infectious diseases. The importance of protecting environmental quality, sustaining biodiversity, and preserving intact ecosystems in carrying out that effort cannot be overemphasized because the concept of "One Medicine" really means "One Medicine---One World--One Health."

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